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(71) Applicant *(for all designated States except US)*: **CEL-SCI CORPORATION** [US/US]; Suite 802, 8229 Boone Boulevard, Vienna, VA 22182 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **TALOR, Eyal, I.** [US/US]; 6603 Deancroft Road, Baltimore, MD 21209 (US).

(74) Agent: **STEINBERG, Richard, A.**; Sherman & Shalloway, 413 North Washington Street, Alexandria, VA 22314 (US).

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(54) Title: PEPTIDE CONSTRUCTS FOR TREATING AUTOIMMUNE AND RELATED DISEASES

(57) Abstract: Conjugated peptides include a first peptide component which is an antigen associated with autoimmune disease, allergy, asthma or transplantation rejection and binds to an antigen-specific receptor on a T cell, and a second peptide component which corresponds to an "antigen presenting molecule" namely, a peptide binding to a T cell surface receptor, which would normally promote T cell activation when the first peptide is bound to its antigen-specific T cell receptor. However, in this invention, the second peptide component has an amino acid sequence which is a modification of an antigen presenting T cell binding peptide, such modification blocking or inhibiting the engagement of receptor sites on the T cell surface (other than the antigen-specific T cell receptor). As a result of the inhibition/blocking, T cell activation is prevented, and is directed through antigen-specific T cell receptor occupation, without T cell activation, leading to antigen-specific T cell anergy and cell death. Administration of the conjugated peptide to an animal, e.g., human, will provide that animal with protection against the disease associated with the first peptide component, resulting from the elimination of the T cells bearing the antigen-specific receptors for that antigenic peptide. The conjugated peptides of this invention provide antigen-specific protection without impairing the immune response to other antigens, including pathogens.

PEPTIDE CONSTRUCTS FOR TREATING AUTOIMMUNE AND RELATED DISEASES

BACKGROUND OF THE INVENTION

(1) Field of Invention

The present invention relates to a conjugated peptide for conferring protection against autoimmune diseases, such as, for example, myocarditis and autoimmune thyroid disease, allergic diseases, asthma, host-versus graft and graft-versus-host disease. The present invention also relates to a method for treating or inhibiting development of autoimmune diseases, asthma, allergy, and tissue transplantation rejection and to conjugated peptides and compositions which may be used to carry out said method.

(2) Background of the Invention

A technique for modulating T cell immunological responses to a wide range of antigenic peptides has been described in the literature. This technology, referred to as LEAPS^{tm}, provides conjugated peptide immunogens (constructs) that modulate both cellular and humoral responses to treat/prevent major diseases, such as HIV infection, herpes simplex virus (HSV) infection, tuberculosis, and the like. The LEAPS constructs are conjugates of two peptides which are linked together covalently. One peptide of the conjugate is an antigen-specific epitope which will bind to the T cell receptor upon recognition. The other peptide of the conjugate is a T cell binding ligand (TCBL) derived from molecules with a known activity, such as, for example, β-2 microglobulin,

IL-1, IL-2, or nonpolymorphic MHC regions, (hereinafter may be referred to as Peptide P_2) and which will engage other sites on the T cells to promote activation of a particular set or subset of T cells. A more detailed discussion of the LEAPS^{tm} technology can be found in the commonly assigned U.S. 5,652,342, to Zimmerman, et al., the disclosure of which is incorporated herein in its entirety by reference thereto.

Briefly, the LEAPS technology allows for the preferential presentation of antigen(s) (peptide sequences) to antigen presenting cells, lymphocytes (T and B cells), dendritic cells, and other cells of the immune system. The antigen presentation is directed in such a way as to affect immune response outcome and determine with some certainty the type of immune response outcome, humoral or cellular. Thus, with the use of certain combinations of appropriate T cell binding peptide molecules together with the appropriate antigen, or the pathogenic molecule(s) of a complex antigen, forming the LEAPS construct, a cellular, antibody, or a mixed immune response can be induced by administration of the LEAPS construct.

While the LEAPS conjugates studied to date were designed to activate the T-cell immunological response to a disease causing antigen, there is also a suggestion in the aforementioned U.S. 5,652,342, that the LEAPS conjugated peptides can activate T suppressor cells or a subset of T suppressor cells, by selection of an appropriate TCBL which will selectively activate, for example, a subset of T suppressor cells.

SUMMARY OF THE INVENTION

It has now been discovered by the present inventor that the TCBL peptide component may be modified to prevent induction of the second signal necessary for the activation of T cells, thereby inhibiting the initiation of an immune response. Thus, the antigenic peptide component of the resulting conjugated peptide will retain its ability to interact with its receptor (antigen-specific binding site) on the T-cell, while at the same time preventing the modified TCBL peptide portion from attaching to the TCBL receptor on the same T cell surface.

By forming a new type of conjugated peptide incorporating such a modified TCBL, instead of cell activation (whether T helper cells, T suppressor cells or other T cells), with an antigenic peptide associated with an autoimmune disease or asthma or allergy, or tissue transplantation rejection, the outcome is shifted from cell activation to inhibition/suppression of the immune response in an antigen specific manner. This outcome is desired due to the fact that antigen-specific response by T cells and other cells may, in many instances, lead to an undesirable immune response outcome culminating in autoimmune disease (in the case of autoantigens), asthma and allergy (in the case of allergens) and transplantation rejection (in the case of transplantation antigens).

Thus, the present invention provides a new class of conjugated peptides comprised of two different covalently bonded peptide components, one peptide component being an antigen associated with autoimmune disease, asthma, allergy or transplantation rejection, and the second peptide component being a T cell binding ligand modified to inhibit or suppress the activation of the class or subclass of T cells to which the antigenic peptide component selectively binds, whereby the conjugated peptide will markedly decrease or completely retard undesirable immune response outcomes (e.g., autoimmune disease, asthma or allergy or transplantation rejection), while maintaining the remainder of the immune response intact.

The peptides useful as the second peptide component, P_3, are themselves novel molecular entities useful in the formation of the peptide constructs of this invention.

The peptide constructs of this invention may be represented by the conjugated peptide of the formula (I)

$$P_1\text{-}x\text{-}P_3 \qquad (I)$$

where P_1 is an antigenic peptide associated with autoimmune disease, asthma, allergy or transplantation rejection and capable of binding to antigen specific T cell receptor molecules on a class or subclass of T cells;

P_3 is a peptide having a sequence corresponding to the sequence of a peptide P_2 after modification of P_2 by addition, deletion or substitution of one or more amino acids or by formation of disulfide bond at one or more sites in the molecule, or a combination thereof, said peptide P_2 being a peptide which is able to bind to accessory molecules on the

surface of said class or subclass of T cells to cause activation thereof when antigen specific T cell receptor molecules on the surface of said class or subclass of T cells bind to said antigenic peptide P_1, whereby attachment of peptide P_3 to the accessory molecule on said T cells or subset of T cells is inhibited; and,

x is a direct bond or a divalent linking group.

The present invention also provides a method for treating or preventing autoimmune disease, asthma, allergy and transplantation rejection, by administering to an animal in need thereof a therapeutically effective amount of a conjugated peptide which includes two different peptide segments covalently linked to each other, directly or via a linker or spacer, wherein a first peptide segment is an antigenic peptide associated with autoimmune disease, asthma, allergy or transplantation rejection, and a second peptide segment is a T cell binding ligand modified to prevent the activation of the T cells or subset of T cells to which the first peptide segment is specifically reactive.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The amino acids in the following sequences may be set forth by the single or three letter identifying symbols as follows:

Amino Acid	Three-letter abbreviation	One-letter symbol
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic Acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic Acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

As far as the present inventor is aware, other than a putative vaccine for Multiple Sclerosis, a disease of the central nervous system, apparently resulting from Myelin Basic Protein activation of T cells, B cells and macrophages, no effective vaccine is currently available for prevention or treatment of autoimmune disease, asthma, allergy or transplantation rejection.

In connection with the LEAPS technology as previously described in the aforementioned U.S. 5,652,342, it is believed that the antigen portion of these constructs interact in a direct manner, primarily to T cells, utilizing the presence of various cell surface molecules and receptors on the T cell. The antigen (in conjunction with the LEAPS molecule) interacts with the antigen-specific T cell receptor on the T cell surface, providing the primary signal - the first of two signals required for T cell activation. The LEAPS molecule,

itself derived from homologous sequences of MHC (HLA) class I and Class II molecules, among others (see, e.g., U.S. 5,652,342) interacts with accessory molecules on the same T cell - providing the secondary signal required for T cell activation. In contrast, according to the present invention, the peptide ostensibly derived from homologous sequences of MHC (HLA) or other T cell binding ligand, is modified to such an extent that the autoimmune disease associated antigenic peptide (or asthma, allergy or transplantation rejection antigen) is still able to interact with the T cell receptor, to provide the primary signal to the T cell, while simultaneously preventing the secondary signal required for T cell activation.

Antigen specific compounds that can protect or treat autoimmune conditions such as myocarditis, or allergy, asthma and transplantation rejection are needed.

Autoimmune myocarditis is a precursor to Dilated cardiomyopathy, an end stage cardiac condition invariably requiring heart transplantation.

My-1 is the myocardiogenic peptide derived from murine cardiac myosin heavy chain (amino acids 334-352), and has been shown to induce severe myocarditis in the A/J strain of mice when injected in the presence of adjuvant (Donermeyer et al 1995, J. Exp. Med. 182:1291-1300).

The present invention was originally developed based, in part, upon the recognition that the LEAPS peptide constructs can be modified to create a new molecular entity which, rather than activating the T cells to which the antigenic peptide portion binds, will inhibit T cell activation and result instead in cell anergy, leading to cell apoptosis and cell death, of those T cells bearing that antigen specific T cell receptor (TCR). That is, the new molecular entity, referred to by the present inventor as "AdapT" construct, when applied to an autoimmune antigenic peptide (e.g., My-1 molecule) will reduce or eliminate the ability of the T cell binding ligand peptide component of the new construct to provide the "second signal" to those T cells, but without effecting the ability of the antigenic peptide component to bind to its target antigen-specific TCR. As a result, the AdapT constructs will still bind, via the antigenic peptide component, to the target T cells (via the antigen specific TCR) but without that T cell, or any of its clones, being activated. Therefore, these antigen specific T cells having TCR occupation, without T cell activation, will undergo anergy and apoptosis, leading to cell death. Since, however, the antigenic specificity is maintained, in this system, using the AdapT constructs (conjugated peptides) only the autoreactive T cells (e.g., those with the My-1 specific T cell receptor on their cell surface) are selected in this negative selection process and will thus be eliminated without harming the efficacy of the remainder of the immune response.

By applying the same technique to other autoimmune disease activating antigenic peptides or to antigenic peptides having a role in causing or initiating asthma and/or allergic reactions, or transplantation rejection, it is similarly possible to selectively cause cell death of only the cells which result in or contribute to autoimmune disease, asthma or allergy, or transplantation rejection, to undergo anergy and apoptosis, to thereby prevent, inhibit or diminish the occurrence of the autoimmune disease, asthma, allergy or transplantation rejection.

The present invention, in one specific aspect thereof, provides novel peptide constructs comprising the myosin peptide (My-1) having the formula:

Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys
Ala Gly Val Tyr Lys SEQ ID NO:1

attached covalently to a modified TCBL, such as, for example, a modified Peptide G ("m-G"), e.g.,

Asn Gly Gln Glu Glu (Xaa) Ala Gly Val
Val Ser Thr Gly Leu Ile SEQ ID NO:2

where Xaa is a direct bond or one or more amino acids replacing Lys;

or a modified Peptide J ("m-J"), e.g.,

Asp Leu Leu Lys Asn Gly Glu Arg
(Xaa) Glu Lys Val Glu SEQ ID NO:3

where Xaa is a direct bond or one or more amino acids replacing Ile;

to form conjugated peptides m-G-x-My-1 (SEQ ID NO:29) or My-1-x-m-G (SEQ ID NO:30), and m-J-x-My-1 (SEQ ID NO:31), or My-1-x-m-J (SEQ ID NO:32) where x is a direct bond or a divalent spacer or linker. Furthermore, in any of these conjugated peptides, the order of the respective amino acid sequences for SEQ ID NOs:1-3, may be reversed from the N- to C-terminals, for example, in the case of m-G-x-My-1, any of the following sequences may be formed:

NGQEEXAGVVSTGLI-x-DSAFDVLSFTAEEKAGVYK SEQ ID NO:29

or ILGTSVVGAXEEQGN-x-DSAFDVLSFTAEEKAGVYK SEQ ID NO:33

or

NGQEEXAGVVSTGLI-x-KYVGAKEEATFSLVDFASD SEQ ID NO:34

or

ILGTSVVGAXEEQGN-x-KYVGAKEEATFSLVDFASD SEQ ID NO:35.

Similarly for any of the other conjugated peptides according to this invention the order of the amino acids in the peptide components, P_1 and/or P_3, may be arranged from the N- to C-terminal or from the C- to N-terminal.

The antigenic portion My-1 of these constructs is immunogenic in several strains of mice and in rabbits. In addition, the non-modified TCBLs G and J as well as the modified TCBLs m-G and m-J, are only poorly immunogenic, as may be judged by the lack of developing antibodies that react to these peptides (G, J, m-G or m-J).

Peptide G is from the beta-2 domain of HLA/MHC class II molecule and Peptide J is from the HLA/MHC Class I beta-2-microglobulin molecule. Other sources of TCBL's include, for example, IL-1, IL-2, IL-12, CD 28, CD40, BB-7, and the like.

exemplary T cell binding ligands and specific sequences thereof. Any of these T cell binding ligands may be selected for modification according to the procedures described herein to form the new conjugated peptides of this invention which will lead to selective cell death of the T cells which bear the antigen-specific cell surface receptor for the specific autoimmune, allergen, or transplantation antigenic peptide component to which the modified TCBL is covalently bound.

In the case of autoimmune diseases, asthma, allergy, and transplantation rejection, the desired outcome is the inhibition/suppression, rather than the stimulation/activation, of the immune response, in an antigen-specific manner. This desired outcome is due to the fact that antigen-specific response by T cells and also B cells may, in many instances, lead to an undesirable immune response outcome, culminating in autoimmune disease (in the case of autoantigens), asthma or allergy (in the case of allergens) and transplantation rejection (in the case of transplantation antigens).

The ability to markedly decrease or completely retard, in an antigen specific manner, undesirable immune response outcomes, while maintaining the remainder of the immune response intact, is achieved through the conjugated peptide constructs of this invention.

The alteration of the "antigen presenting molecule" (TCBL) forming one peptide sequence component of the constructs of this invention provides for the enhancement of the antigen interaction with the antigen-specific T cell receptor. In particular, the changes (alterations) are made in those portion(s) of these antigen presenting molecule(s), which are responsible for delivering the second signal (required for T cell activation). That is, the modified TCBLs according to this invention are modified in such a way so as to lead to T cell receptor occupation (by the, e.g., autoimmune antigenic peptide, antigen associated with asthma or allergy or transplantation antigen) without T cell activation.

The occupation of the antigen-specific T cell receptor, on the T cell surface, without the availability- or with the active blockade- of a second signal to the antigen-specific T cell, leads to T cell anergy, T cell apoptosis and, eventually, cell death. Using the appropriate antigen, together with the modified antigen presenting molecule (forming the desired peptide construct) it becomes possible to preferentially remove/purge, in an antigen-specific manner, only the autoantigen, asthma, allergy or transplantation antigen reactive/causing T cell clones from humans and other animals (e.g., mammals).

The advantage of this system is that, by the administration of these constructs, antigen-specific autoreactive, asthma and allergy, and transplantation antigen reacting/causing T cell clones are removed from the host. This removal of only the disease causing cells renders the host unable to interact and respond only to disease promoting/inducing/causing antigens, while at the same time maintaining an intact immune response (necessary for maintaining the host's health) to all other antigens (including other pathogens).

This invention provides a new T cell modulation platform technology designed to synthesize novel peptide constructs that arrest/modify both cellular and humoral immune responses, and is directed towards the treatment or prevention of major diseases such as autoimmune disease, asthma, allergy and transplantation rejection.

When applied to transplantation rejection in individuals undergoing tissue, e.g., organ, transplantation, the present invention is applicable to both host-versus-graft (HvG) and graft-versus-host (GvH) rejections. In the case of HvG, the host immune response T cells are activated by donor antigens (e.g., HLA antigens and other non-HLA antigens) that are specific for the donor cells and which the host perceives as "foreign." The host immune cells attack the donor organ resulting in graft rejection. In the case of GvH, the donor

cells, especially as a result of bone marrow transplantation, respond to the "foreign" host cells/organ antigens resulting in infiltration of the host's organ(s), by donor lymphocytes culminating in multiple organ failure and, often, death.

The peptide constructs of this invention may be represented by the conjugated peptide of the formula (I)

$$P_1\text{-}x\text{-}P_3 \qquad (I)$$

where P_1 is an antigenic peptide associated with autoimmune disease, asthma, allergy or transplantation rejection and capable of binding to antigen specific T cell receptor molecules on a class or subclass of T cells;

P_3 is a peptide having a sequence corresponding to the sequence of a peptide P_2 after modification of P_2 by addition, deletion or substitution of one or more amino acids or by formation of disulfide bond at one or more sites in the molecule, or a combination thereof, said peptide P_2 being a peptide which is able to bind to accessory molecules on the surface of said class or subclass of T cells to cause activation thereof when antigen specific T cell receptor molecules on the surface of said class or subclass of T cells bind to said antigenic peptide P_1, whereby attachment of peptide P_3 to the accessory molecule on said T cells or subset of T cells is inhibited; and,

x is a direct bond or a divalent linking group.

As will be appreciated from Formula (I), the peptide constructs (AdapT constructs) of this invention, include two or more peptides, which are linked together covalently. The peptide constructs may be synthesized either in vitro, e.g., by genetic engineering techniques, or by chemical peptide synthesis techniques, either as one conjoined molecule, or separately as individual molecular entities followed by covalent bonding at specific sites. One peptide of this construct, peptide P_1, is a specific epitope (antigen or pathogenic epitope), which will bind to the antigen-specific T cell receptor upon recognition. Representative, non-limiting examples of such peptides, suitable as P_1, in the present invention, include, Peptide My-1: Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala Gly Val Tyr Lys (SEQ ID NO:1); TNF amino acid sequence 70-80: Pro Ser Thr His Leu Val Leu Ile Thr His Thr Ile (SEQ ID NO:4); Rheumatoid arthritis collagen Type II, amino acid sequence 390-402: Ile Ala Phe Lys Gly Glu Gln Gly Pro Lys Gly (SEQ ID NO:5); Multiple Sclerosis Myelin proteolipid (MPL) amino acid sequence: Lys Asn Ile Val Thr Pro Arg Thr (SEQ ID NO:6); Peptide associated with spontaneous thrombosis amino acid sequence: Gly Asp Lys Val Ser Phe Phe Cys Lys Asn Lys Glu Lys Lys Cys (SEQ ID NO:7); amino acid residues 8-15: Val Ala Asn Leu Leu Glu Asn Tyr (SEQ ID NO:8) or 125-147: Lys Ser Tyr Cys Glu Ile Ile Val Thr His Phe Pro Phe Asp Gln Gln Asn Cys Thr Met Lys Leu Gly (SEQ ID NO:9) or 195-215: Asp Thr Pro Tyr Leu Asp Ile Thr Tyr His Phe Ile Met Gln Arg Ile Pro Leu Tyr Phe Val (SEQ ID NO:10) of the acetylcholine receptor (α-subunit)

associated with Myasthenia Gravis. These and other autoimmune, allergy, asthma and transplantation rejection diseases or conditions, and associated antigens, may be found in the literature, and reference is made to, for example, Clinical Laboratory Immunology, Kenneth D. McClatchey, Ed., Williams & Wilkins (USA), 1994; Clinical Immunology Principles and Practice (Volumes I and II), Robert R. Rich, Ed. in Chief, Mosby (USA), 1996; Manual of Clinical Laboratory Immunology (5th Edition), Noel R. Rose, Ed., ASM Press (USA), 1997; and Inflammation Basic Principals and Clinical Correlates (3rd Edition), John I. Gallin and Ralph Snyderman, Eds., Lippincott Williams & Wilkins (USA), 1999.

The other peptide, Peptide P_3, is a modified T cell binding ligand derived from molecules (TCBLs) with a known affinity to cell surface receptors present on T cells. The modified TCBL may be referred to hereinafter, for convenience, as the "AdapT molecule." Suitable sources (P_2) for the AdapT molecule, P_3, include, but are not limited to, the following; β-2 microglobulin, IL-1, IL-2, IL-7, IL-15, CD28, CD40, BB-7, and nonpolymorphic MHC regions - which, when modified, inhibit the engagement of receptor sites (other than the T cell receptor) on the T cell surface - that, would otherwise, if engaged, promote T cell activation.

Therefore, the occupation of the T cell receptor and the simultaneous blockade or inhibition of interaction of the different ligands with these secondary, - signal transducing - cell surface molecules will cause T cell anergy, cell apoptosis and lead to cell death. As these diseases

(autoimmune, asthma, allergy, transplantation rejection, e.g., HvG and GvH) are caused, primarily, by the activation of antigen-specific clones of T cells (and also through B cell activation, which is dependent on T cell help), the selective removal of these clones will render the host unable to respond to these antigens. This, in turn, will result in the treatment and may lead to the cure or elimination or down regulation of these types of diseases.

MODIFICATIONS OF THE TCBL (The AdapT Molecules)

The following are examples of types of molecular modifications to the antigen presenting molecule, TCBL, (also referred to as Peptide P_2) which will provide the AdapT molecule (P_3) which will result in the blockade or inhibition of a second signal to the antigen-specific T cell clones as described above:

1. Single or few amino acid deletion(s);

2. Single or few amino acid substitution(s) and/or addition(s);

3. Disulfide bond formation at specific site(s) in the antigen presenting molecule;

4. Combination of any and all of the changes listed in 1, 2, and 3 above;

5. An amino acid sequence (R) of at least 4 amino acids, preferably at least 6 amino acids, more preferably at least about 8 or 9 amino acids, such as from about 10 to about 50

amino acids, and wherein "R" will not bind to the antigen of interest, herein P_1, and will not interact with the T cell accessory molecule(s) in such a way that would cause T cell activation when the TCR is engaged by P_1.

The specific amino acid modifications (deletions, additions and/or substitutions) in 1, 2 and 3 above, are selected on the premise that homologous regions, in these molecules, are those most important for the overall functional integrity of these molecules. Thus, a comparison of, for example, the molecular protein structure of the HLA Class I and Class II molecular fragments derived from the intact molecules, among different species, have revealed different domains, within the structure of these molecules, that share molecular motifs. Similar observations apply to the other source molecules identified above, or any other source molecules of TCBLs.

For example, a comparison of the Human HLA Class I β-2 microglobulin molecule at positions 38 to 50 of the intact molecule, and those found in Rabbit, mouse, and guinea pig (for example), reveals homologous amino acid sequence at positions 40 to 43, 46, 49, and 50. In position 38, Mouse and Guinea Pig share the same amino acid (Glutamic acid), and in position 47, Humans and Rabbits share the same amino acid (Glutamic acid).

Based on the above, the rational place to modify these molecules is at the positions of homology in the specific sequence of this molecule. Specifically, a modification of the Class I β-2 microglobulin molecular peptide (Peptide J)

(aa 38 to 50) at positions 40 to 43 (...Leu – Lys – Asn – Gly...) and/or at position 46 (...Ile...) and 47 (...Glu...), by substitution, addition and/or deletion of one or more amino acids, will effectively prevent or inhibit the modified peptide J from attaching to the accessory molecule on the surface of the T cells or subset of T cells containing the antigen specific T cell receptor molecules for peptide P_1.

Similarly, changes in position(s) of homology (i.e., conserved amino acids) in the β2 domain of the HLA Class II molecule (Peptide G) positions 135 to 149 of the intact molecule at positions 138 to 141 will result in modification of Peptide G which will prevent T cell activation when the antigenic peptide sequence (P_1) is bound to the antigen specific T cell receptor on the appropriate class or subclass of T cells. Preferably, the β2 domain HLA Class II molecule, Peptide G, is modified by substitution, addition or deletion of one or more amino acids at aa 138 to 141 (...Glu – Glu – Lys – Ala...).

For amino acid additions and substitutions, one or more than one of the conserved amino acids will be replaced by one or more amino acids. When a conserved amino acid is replaced by more than one amino acid, the replacement amino acids (preferably no more than about 15, preferably no more than about 10, especially, no more than about 5 or 6, such as 2 or 3) may be inserted in the amino acid sequence. The amino acids substitutions may also be added as side chain attachments bonded to, or replacing, one of the conserved amino acids. While the specific sequence of the added

internal or side chain replacement amino acids is not particularly critical, care should be taken to select a sequence which will not bind or interact with the sequence P_1 and will not interact with the T cell accessory molecule(s) on the particular set or subset of T cells bearing the antigen specific TCR for P_1 to inadvertently cause T cell activation when the TCR is engaged by P_1. For any given peptide P_1 the skilled practitioner will be able to determine suitable sequences for amino acid substitutions and/or additions. Usually, however, it should be sufficient to simply delete or replace one or more of the conserved (homologous) amino acids from the TCBL sequence. When replacing the conserved amino acid with a single amino acid it is generally preferred to select an amino acid having diverse properties and/or molecular size from as that of the conserved amino acid being replaced. For example, an acidic amino acid may be replaced with a basic amino acid. Other types of "non-conservative" types of amino acid substitutions are well known to the skilled practitioner.

As representative, non-limiting, examples of modifications according to 1 above, the following may be mentioned, using the TCBLs Peptide G and Peptide J as specific embodiments of peptide P_2.

Type 1-(a) single amino acid (aa) deletion

For Peptide G:

(1) delete Glu (aa138);

(2) delete Glu (aa139);

(3) delete Lys (aa140);

(4) delete Ala (aa141).

For Peptide J:

(1) delete Leu (aa40);

(2) delete Lys (aa41);

(3) delete Asn (aa42);

(4) delete Gly (aa43);

(5) delete Ile (aa46);

(6) delete Glu (aa47).

Type 1-(b) few amino acid deletions

For Peptide G:

(1) delete Glu-Glu (aa138-139)

(2) delete Glu-Lys (aa139-140)

(3) delete Glu (aa138) and Lys (aa140)

(4) delete Glu (aa138) and Ala (aa141)

(5) delete Glu (aa139), Lys (aa140) and Ala (aa142).

For Peptide J:

(1) delete Leu (aa40) and Lys (aa41);

(2) delete Leu (aa40) and Ile (aa46);

(3) delete Lys (aa41) and Asn (aa42);

(4) delete Ile (aa46) and Glu (aa47).

Type 2-(a) single amino acid substitution or insertion

For Peptide G:

(1) replace Glu (aa138) with Ala or Ile or Leu or Val or Gly or Phe or Tyr or Thr or Ser or Lys or Arg or His or Asn or Gln;

(2) insert Ile or Leu or Val or Gly or Ala or Phe or Tyr or Thr or Ser or Lys or Arg or His or Asn or Gln after Glu (aa139);

(3) insert Glu or Asp or Ser, etc., after Lys (aa140);

(4) insert Gly or Tyr or Lys, etc., after Ala (aa141);

(5) replace Lys (aa140) with Gly or Val or Pro or Thr or Tyr or Asp or Asn, etc.

For Peptide J:

(1) insert Asn after Leu (aa40);

(2) insert Leu after Gly (aa41);

(3) insert Ile after Asn (aa42);

(4) insert Glu after Gly (aa43);

(5) insert Gly after Ile (aa46);

(6) insert Asn after Glu (aa47).

(7) replace Gly (aa41) with Pro or Ser or Thr or Phe or Tyr or Trp or Lys or Arg or His or Asp or Glu or Asn or Gln.

Type 2-(b) multiple (few) amino acid substitutions/insertions

For Peptide G:

(1) insert Ala-Lys after or for Glu (aa138);

(2) insert Glu-Lys after Lys (aa140);

(3) insert Asp-Glu-Arg after or for Lys (aa140);

(4) insert Gly-Ala after or for Lys (aa140);

(5) insert Glu after Glu (aa138) and insert Lys after Ala (aa1410;

(6) insert Gly after Glu (aa139) and insert Lys after Lys (aa140);

(7) insert Ile, Glu and Gly after Glu (aa139), Lys (aa140) and Ala (aa141), respectively;

(8) replace Glu (aa139) with Tyr and insert Ser-Ala after Lys (aa140).

For Peptide J:

(1) insert Ile after Leu (aa40) and insert Gly after Lys (aa41);

(2) insert Asn after Lys (aa41) and insert Glu after Asn (aa42);

(3) insert Leu and Gly after aa42 and 43, respectively;

(4) insert Ile and Glu after aa 43 and 46, respectively;

(5) insert Lys and Leu after aa46 and aa47, respectively;

(6) insert Glu and Leu after aa 40 and 46, respectively;

(7) replace Leu (aa40) with Lys or Tyr and replace Ile (aa46) with Ala or Thr;

(8) replace Asn (aa41) with Asp-Ala;

(9) replace Ile (aa46) with Glu and insert Ala after Gly (aa43).

Type 3-(a) Disulfide bond formation

For Peptide G:

(1) insert sulfhydryl groups, e.g., Met or Cys, between Asn (aa135) and Gly (aa136) and between Lys (aa140) and Ala (aa141) and form a disulfide bond;

(2) insert Cys or Met between Gly (aa136) and Gln (aa137) and between Ala (aa141) and Gly (aa142) and form a disulfide bond;

(3) insert Cys or Met between Asn (aa135) and Gly (aa136) and between Gly (aa142) and Val (aa143) and form a disulfide bond;

For Peptide J:

(1) insert sulfhydryl groups, e.g., Cys or Met between Asn (aa42) and Gly (aa43) and between Asp (aa38) and Leu (aa39) and form a disulfide bond;

(2) insert Cys or Met between Asp (aa38) and Leu (aa39) and between Gly (aa43) and Glu (aa44) and form a disulfide bond;

(3) insert Cys or Met between Glu (aa44) and Arg (aa45) and between Leu (aa39) and Leu (aa40) and form a disulfide bond;

(4) insert Met or Cys between Arg (aa45) and Ile (aa46) and between Asp (aa38) and Leu (aa39) and form a disulfide bond.

The modification in type 5 above is actually a specific example of amino acid addition/substitution according to type 2 above where "R" represents an amino acid sequence of at least 4 amino acids, preferably at least 6 amino acids, more preferably at least about 8 or 9 amino acids, such as from about 8 to about 50 amino acids, more preferably from about 10 to about 20 amino acids, and wherein "R" will not bind to the antigen of interest, herein P_1, and will not interact with the T cell accessory molecule(s) in such a way that would cause T cell activation when the TCR is engaged by P_1.

The "R" modifying group may be linked to the free terminal end of the non-modified TCBL peptide, P_2, or R may be linked to an already modified TCBL wherein the modification is at a different site than that to which R is to be linked. R may also be linked to an internal amino acid of P_2 (preferably,

one of the "conserved" amino acids) or R may be linked to an amino acid substitution for a conserved amino acid, or R may be inserted between two internal amino acids of P_2, usually and preferably, at a position located at least about 2, preferably at least about 4 amino acids from either the N- or C- terminal of P_2.

Examples of modifying groups R, include, for example, a portion of beta-pleated sheet of MHC Class I, and a portion of the alpha-helical structure of MHC Class I, (see "Fundamental Immunology" W. E. Paul, Raven Press (USA) 1986).

As an example of the beta-pleated sheet modifying group R, mention may be made of, for example, the amino acid sequence at positions (residues) 95-118:

Leu Gln Ser Met Tyr Gly Cys Asp Val Gly
Pro Asp Gly Arg Leu Leu Arg Gly His Asp
Gln Tyr Ala Ile SEQ ID NO:12

The entirety of the sequence SEQ ID NO:12 or a portion thereof, usually of at least about 8, preferably, at least about 10 consecutive amino acids, such as, for example, positions 99-113:

Tyr Gly Cys Asp Val Gly Pro Asp Gly Arg
Leu Leu Arg Gly His SEQ ID NO:13

positions 96-111:

Gln Ser Met Tyr Gly Cys Asp Val Gly Pro
Asp Gly Arg Leu Leu Arg SEQ ID NO:14

or positions 100-118:

Gly Cys Asp Val Gly Pro Asp Gly Arg Leu
Leu Arg Gly His Asp Gln Tyr Ala Ile SEQ ID NO:15

or positions 100-115:

Gly Cys Asp Val Gly Pro Asp Gly Arg Leu

Leu Arg Gly His Asp Gln SEQ ID NO:36

may be attached to the TCBL, P_2, at a terminal thereof (the end not bonded to P_1) directly or via linker or spacer x or the R modifying group may be linked to or replace an internal amino acid or inserted between two adjacent internal amino acids of P_2 (thus forming a branch or side chain group), preferably one of the homologous (conserved) amino acids as described above, and preferably spaced by at least 2, preferably at least 4, amino acids from the N- or C-terminal of P_2.

As an example of a portion of the alpha-helical structure of MHC Class I, mention may be made of, for example, the amino acid sequence at residues 64-87:

Thr Gln Ile Tyr Lys Ala His Ala Gln Thr

Asp Arg Glu Ser Leu Arg Asn Leu Arg Gly

Tyr Tyr Asn Gln SEQ ID NO:16

or a portion thereof, usually at least about 8 amino acids, such as, for example, residues 64-79 having the sequence

Thr Gln Ile Tyr Lys Ala His Ala Gln Thr

Asp Arg Glu Ser Leu Arg SEQ ID NO:17

or residues 79-87 having the sequence

Arg Asn Leu Arg Gly Tyr Tyr Asn Gln SEQ ID NO:18

These R groups may, similarly, be linked to the unoccupied (free) terminal of P_2. Alternatively, to form a side or branched chain on P_2, the R group may be linked to an

internal amino acid or substituted internal amino acid in P_2. When the R group replaces an internal amino acid, it preferably replaces a conserved amino acid in the TCBL sequence, P_2, or still further, one of the amino acids of the R group, preferably the N- or C-terminal amino acid of R, may be inserted between two adjacent amino acids in P_2. The side chain R group will preferably be spaced by at least 2, preferably at least 4 amino acids from the N- or C-terminal amino acid of P_2. Representative examples of R group modifications to form the AdapT molecule P_3 include, for example, in the case of Peptide G, insertion of R between amino acid residues at positions 135 and 136, between positions 136 and 137, between positions 137 and 138, between positions 138 and 139 and/or between positions 139 and 140; or addition of the R group to Asn at aa position 135 or to Ile at position 149 or to an internal amino acid, such as to Glu at aa138 or aa139. Still further, the R group may be inserted in place of an internal amino acid, such as at positions 138, 139, 140 or 141.

The peptide construct according to modification 5 above, may be represented by the following formula (II):

$$P_1\text{-}x\text{-}(P_2\text{-}R) \qquad \text{(II)}$$

where P_1, P_2, R and x are as previously defined, and (P_2-R = P_3) and where R may be linked to the free terminal amino acid of P_2 or R may substitute for or be linked to an internal amino acid of P_2. Thus, P_2-R may take the form (A1) a_1-a_2-...a_n-R (where a_1, a_2, a_n represent the first, second and nth amino acids in the amino acid sequence of P_2, and where a_1 represents the

terminal amino acid linked to P_1 directly or via x, and a_n represents the free or unoccupied terminal amino acid) or P_2R may take the form (A2) a_1-....a_m(R)....a_n, where a_1 and a_n have the same meanings as above and a_m represents an internal amino acid of P_2 or a substituted amino acid for the mth amino acid in the sequence of P_2 or an amino acid of R.

For example, in the case of Peptide G, having the amino acid sequence (single letter format): NGQEEKAGVVSTGLI (SEQ ID NO:11) and R being taken from amino acid (aa) positions 95-118 (A_{95-118}) (SEQ ID NO:12) or aa positions 99-113 (A_{99-113}) (SEQ ID NO:13) or aa positions 96-111 (A_{96-111}) (SEQ ID NO:14) or aa positions 100-118 ($A_{100-118}$) (SEQ ID NO:15) of the beta-pleated sheet of MHC Class I representative AdapT molecules (P_3) according to the invention include the following:

ILGTSVVGADEEQGN-x_1-LQSMYGCDVGPDGRLLRGHDGYAI (III) SEQ ID NO:19
Peptide G linker A_{95-118}

or

NGQEEDAGVVSTGLI-x_1-LQSMYGCDVGPDGRLLRGHDGYAI (III-1) SEQ ID NO:20
Peptide G linker A_{95-118}

or

NGQEEDAGVVSTGLI-x_1-IAYGDHGRLLRGDPGVDCGYMSQL (III-2) SEQ ID NO:21
Peptide G linker A_{95-118}

or

ILGTSVVGADEEQGN-x_1-IAYGDHGRLLRGDPGVDCGYMSQL (III-3) SEQ ID NO:22
Peptide G linker A_{95-118}

where x_1 represents a divalent spacer, such as, for example, GGG, GGGGS, and the like; or

NGQEEDAGVVSTGLI
|
$A_{100-115}$ (IV) SEQ ID NO:23

NGQEEDAGVVSTGLI
| |
| A_{99-113}
A_{95-118}

(V) SEQ ID NO:24

NGQEELKAGVVSTGLI
|
A_{96-118}

(VI) SEQ ID NO:25

In formula (VI), the first leucine (L) corresponds to the amino acid residue 95 of SEQ ID NO:12 inserted between the Glu (E) and Lys (K) amino acid residues of Peptide G.

In the above formulas for representative AdapT molecules P_3, the peptide of formula (III) will preferably be linked to P_1 (directly or via divalent linker or spacer x) via the free terminal {Ile (I) or Asn (N)} amino acid. The AdapT molecules represented by formulas (IV), (V) and (VI) may be linked to P_1 at either the Asn (N) or the Ile (I) terminal amino acids. In this regard, it should be understood that the order of the C- and N- terminals of any of these peptide sequences can be reversed

Thus, conjugated peptides effective for treating myocarditis, for example, can have any of the following representative formulas incorporating My-1 (SEQ ID NO:1):

A_{95-118}-GGGGS-NGQEEKAGVVSTGLI-GGG-KYVGAKEEATFSLVDFASD

SEQ ID NO:26

NGQEEDAGVVSTGLI-GGG-DSAFDVLSFTAEEKAGVYK
|
A_{99-113}

SEQ ID NO:27

NGQEEDAGVVSTGLI-GGG-DSAFDVLSFTAEEKAGVYK
| |
| A_{99-113}
$A_{100-118}$

SEQ ID NO:28

In each case, however, the side chain beta-pleated amino acid sequence will not interfere with the attachment of P_1 to its TCR but will prevent, or at least greatly inhibit, attachment of the modified TCBL (AdapT molecule) to the T cell accessory molecules on the surface of that T cell and its clones, thereby preventing (or at least substantially diminishing) T cell activation in an antigen-specific manner.

The peptide constructs according to this invention as well as the individual components P_1 and P_3, (including P_2 and R) may be formed by any of the known techniques for forming peptides, including, for example, solid phase peptide synthesis, such as described, for example, by Merrifield, R. B., 1963, J. of Am. Chem. Soc., 85:2149-2154. It is also within the scope of the invention to produce the individual peptides and/or peptide conjugates by genetic engineering based on the corresponding gene sequences. Reference may also be had, for example, to the aforementioned U.S. 5,652,342, for further details as to synthesis methods.

There is also no particular restriction on the size of the individual peptides P_1 or P_3, provided however, that the minimum length will usually be at least 4, and preferably at least 6, such as about 8 or 9 amino acids, usually no more than about 20 amino acids, for peptide P_1, which will allow binding to the antigen specific binding site, and similarly, for peptide P_3 to effectively block/inhibit binding to the accessory molecule.

Where the individual peptide components or the peptide construct are longer than about 40 amino acids, especially longer than about 50 amino acids, it will often be necessary and preferred, in the case of solid phase peptide synthesis, to synthesize individual consecutive lengths of no more than about 40 amino acids, preferably no more than about 30 amino acids, and then covalently link the consecutive sections by techniques well known in the art, such as, for example, the aforementioned U.S. 5,652,342.

There is also no particular restriction on the total length of the peptide constructs of this invention but, they will usually be at least about 20 amino acids in length, preferably at least about 25 to 30 amino acids in length and usually no longer than about 300 amino acids, preferably up to about 200 or more amino acids, especially preferably, from about 20 to about 200 amino acids, more preferably from about 20 to about 100 amino acids, such as, for example, from about 30 to 80 amino acids, more preferably form about 30 to 60 amino acids.

The peptide constructs of this invention may be used as therapeutic compounds for the treatment of automimmmune diseases and conditions, and for treatment of allergy and asthma and transplantation rejection in humans and other animals, preferably mammals, including household pets, such as dogs and cats, as well as livestock, such as bovine, porcine and equine. The peptide constructs may also be used

prophylactically in humans and other animals to inhibit the likelihood of onset of autoimmune disease, allergy or asthma in individuals considered to be at risk for such conditions, whether as a result of genetic factors or environmental exposure, age or other factors.

The peptide conjugates may be administered alone (in a suitable vehicle depending on the mode of administration) or in combination or in conjunction with an adjuvant or other active component, including, for example, any conventional treatment therapy for the particular condition to be treated.

Preparations containing the subject peptide constructs may be administered by any of the known methods for peptide administration, including, for example, intramuscularly (IM), subcutaneously (SC), transdermally, or intranasally or orally, or as an inhalant preparation or intravenously. These preparations may be formulated as unit dosages to provide a therapeutically effective amount of the conjugated peptide, preferably an amount in the range of 10 to 100 micrograms per kilogram of body weight. Usually, the therapeutic or prophylactic preparations will be administered over a prolonged course of administration, such as weekly, bi-weekly, monthly, quarterly, semi-annually or annually, often for a patient's lifetime. The prolonged treatment will generally be necessary since newly formed or mature T cells with the antigen-specific TCR of interest, can be expected to be produced by the bone marrow and re-enter into the blood and lymphatic system, even after the initial treatment, over the course of an individual's lifetime.

The peptide constructs of this invention are also useful in connection with prevention or inhibition of transplantation rejection in animals (humans and other mammals) undergoing tissue or organ transplantation. Such transplantation rejection may take the form of host-versus-graft (HvG) rejection or as graft-versus-host (GvH) rejection, the latter being especially severe in immunocompromised and severely immunosuppressed individuals.

In the case of HvG, the host immune response cells, T cells, B cells, and macrophages, are activated by donor antigens (e.g., HLA antigens and other non-HLA antigens) that are specific for the donor cells and which the host perceives as "foreign." The host immune cells attack the donor organ resulting in graft rejection.

In the case of GvH, the donor cells (especially as a result of bone marrow transplantation) respond to the host's cells/organs(s) as foreign antigens resulting in cellular infiltration of the host's organs, culminating in multiple organ failure, and often, death.

The use of the peptide constructs of this invention, for treatment of GvH, wherein P_1 is a transplantation antigen, e.g., a sequence derived from the host antigens (e.g., HLA class II, HLA class I and other host specific antigens) may be mixed with donor bone marrow cells prior to infusion. The resulting cell preparation is then administered, such as by intravenous infusion, to the recipient. The mixture of donor specific peptide construct(s) may be infused separately into the recipient following bone marrow engagement

(transplantation) every other day for 2 to 3 weeks. This treatment will cause only those bone marrow donor cells that may be sensitized to the host cell antigens to undergo anergy, apoptosis and cell death, thereby inhibiting or diminishing GvH disease.

For treating transplantation rejection in the case of organ donation, i.e., HvG, the host may be injected with from about 10 to about 100 micrograms per kilogram of body weight with peptide construct(s) using as P_1 unique antigen(s) of the donor specific organ antigen, or preferably, a mixture of different donor specific antigens P_1. In this case, the different P_1's may be linked to the same or different AdapT molecules, P_3, for example, as P_{1a}-x-P_3 + P_{1a}-x-P_3. etc., or as P_{1a}-x_1-P_{1b}-x_2-P_3 or P_{1a}-x_1-P_3-x_2-P_{1b}, etc. Dosage amounts and modes of administration are similar to the dosages and modes of administration for GvH, namely, for example, about 10 to 100 micrograms/kilogram body weight, via intravenous infusion, every other day for 2 to 3 weeks, and then monthly, bi-monthly, semi-annually or annually, thereafter, in the recipient following organ transplantation. This treatment will result in depletion of the recipient's immune T cells which would otherwise be available to react with donor organ antigens, leading to the inhibition of host-vs-graft rejection.

WHAT IS CLAIMED IS:

Claim 1. A conjugated peptide of the formula (I)

$$P_1\text{-}x\text{-}P_3 \qquad (I)$$

where P_1 is an antigenic peptide associated with autoimmune disease, asthma, allergy or transplantation rejection, and capable of binding to antigen specific T cell receptor molecules on a class or subclass of T cells;

P_3 is a peptide having a sequence corresponding to the sequence of a peptide P_2 after modification thereof by addition, deletion or substitution of one or more amino acids or by formation of disulfide bond at one or more sites in the molecule, or a combination thereof, said peptide P_2 being a peptide which is able to bind to accessory molecules on the surface of said class or subclass of T cells to cause activation thereof when the antigen specific T cell receptor molecules on the surface of said class or subclass of T cells bind to said antigenic peptide P_1, whereby attachment of peptide P_3 to the accessory molecule on said T cells or subset of T cells is inhibited; and,

x is a direct bond or a divalent linking group.

Claim 2. The conjugated peptide of claim 1 wherein the peptide P_2 comprises an amino acid sequence including residues 38 to 50 of Human HLA Class I β-2 microglobulin and wherein the peptide P_3 comprises the sequence of P_2 modified by substitution, addition or deletion of at least one of residues 38 to 43, 46 and 47.

Claim 3. The conjugated peptide of claim 1 wherein the peptide P_2 comprises an amino acid sequence including residues 135 to 149 of the β2 domain of the human HLA Class II molecule and wherein the peptide P_3 comprises the sequence of P_2 modified by substitution, addition or deletion of at least one of residues 138 to 141.

Claim 4. The conjugated peptide of claim 1 wherein peptide P_1 comprises the myocarditogenic peptide of SEQ ID NO:1.

Claim 5. The conjugated peptide of claim 1 wherein peptide P_1 comprises an antigenic peptide selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10.

Claim 6. The conjugated peptide of claim 1 wherein peptide P_3 is a peptide comprising the sequence of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:16, SEQ ID NO:17, and SEQ ID NO:18.

Claim 7. The conjugated peptide of claim 1 having in total from about 20 to about 200 amino acids.

Claim 8. The conjugated peptide of claim 1 consisting of the sequence of SEQ ID NOs:19, 20 and 21.

Claim 9. A pharmacological composition comprising a conjugated peptide as set forth in claim 1 and a pharmacologically effective carrier.

Claim 10. A method for treating or inhibiting development of autoimmune disease, asthma, allergy or transportation rejection which comprises administering to a mammal in need thereof a therapeutically effective amount of a conjugated peptide having the formula (I)

P_1-x-P_3 (I)

where P_1, P_3, and x are as defined in claim 1.

Claim 11. A peptide having SEQ ID NO:2 or SEQ ID NO:3.

Claim 12. A peptide having SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24 or SEQ ID NO:25.

Claim 13. A peptide according to claim 1 having SEQ ID NO:26, SEQ ID NO:27 or SEQ ID NO:28.

Claim 14. A conjugated peptide having the formula

DSAFDVLSFTAEEKAGVYK-x-NGQEEXAGVVSTGLI SEQ ID NO:30

or

NGQEEXAGVVSTGLI-x-DSAFDVLSFTAEEKAGVYK SEQ ID NO:29

or

DLLKNGERXEKVE-x-DSAFDVLSFTAEEKAGVYK SEQ ID NO:31

or

DSAFDVLSFTAEEKAGVYK-x-DLLKNGERXEKVE SEQ ID NO:32

where x is a direct bond or a divalent linker and X in SEQ ID NO:29 and SEQ ID NO:30 represents an amino acid other than Lys or a sequence of two or more amino acids; and in SEQ ID NO:31 and SEQ ID NO:32, X represents an amino acid other than Ile or a sequence of two or more amino acids.

Raw Sequence Listing

Sequence Listing

(1) GENERAL INFORMATION

(i) APPLICANTS:CEL-SCI CORPORATION

(ii) TITLE OF INVENTION:PEPTIDE CONSTRUCTS FOR TREATING AUTOIMMUNE AND RELATED DISEASES

(iii) NUMBER OF SEQUENCES:36

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE:Law Office of Sherman and Shalloway

(B) STREET:413 N. Washington Street

(C) CITY:Alexandria

(D) STATE:Virginia

(E) COUNTRY:USA

(F) ZIP:22314

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE:Diskette, 5.25 inch, 360 kb storage

(B) COMPUTER:Dell System 210; Intel 80 286 Microprocessor

(C) OPERATING SYSTEM:MS DOS 6.2

(D) SOFTWARE:Word Perfect, Version 5.1

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:UNASSIGNED

(B) FILING DATE:CONCURRENTLY HEREWITH

(vii) ATTORNEY/AGENT INFORMATION:

(A) NAME:Richard A. Steinberg

(B) REGISTRATION NUMBER:26,588

(C) REFERENCE/DOCKET NUMBER:CS-110/PCT

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE:(703) 549-2282

(B) TELEFAX:(703) 836-0106

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:19

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:myosin peptide My-1

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:1:

Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala
5 10 15
Gly Val Tyr Lys

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:15

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:myosin peptide My-1

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 6 is direct bond or a single amino acid other than Lys or multiple amino acid residues

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:2:

Asn Gly Gln Glu Glu Xaa Ala Gly Val Val Ser Thr Gly Leu Ile
5 10 15

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:13

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:myosin peptide My-1

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 9 is a direct bond or a single amino acid other than Ile or multiple amino acid residues

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:3:

Asp Leu Leu Lys Asn Gly Glu Arg Xaa Glu Lys Val Glu
5 10

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:12

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:tumor necrosis factor TNF

(B) LOCATION:70-80

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:4:

Pro Ser Thr His Leu Val Leu Ile Thr His Thr Ile
5 10

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:11

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:rheumatoid arthritis collagen type II

(B) LOCATION:390-402

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:5:

Ile Ala Phe Lys Gly Glu Gln Gly Pro Lys Gly
5 10

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:8

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:mutiple sclerosis myelin proteolipid

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:6:

Lys Asn Ile Val Thr Pro Arg Thr
5

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:15

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:7:

Gly Asp Lys Val Ser Phe Phe Cys Lys Asn Lys Glu Lys Lys Cys
5 10 15

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:8

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(ix) FEATURE:

(A) NAME/KEY:acetylcholine receptor, α-subunit

(B) LOCATION:8-15

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:8:

Val Ala Asn Leu Leu Glu Asn Tyr
5

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:23

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:acetylcholine receptor, α-subunit

(B) LOCATION:125-147

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:9:

Lys Ser Tyr Cys Glu Ile Ile Val Thr His Phe Pro Phe Asp Gln
5 10 15
Gln Asn Cys Thr Met Lys Leu Gly
20

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:21

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:acetylcholine receptor, α-subunit

(B) LOCATION:195-215

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:10:

Asp Thr Pro Tyr Leu Asp Ile Thr Tyr His Phe Ile Met Gln Arg
5 10 15
Ile Pro Leu Tyr Phe Val
20

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:15

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:11:

Asn Gln Gly Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu Ile
5 10 15

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:24

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:beta-pleated sheet of MHC Class I

(B) LOCATION:95-118

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:12:

Leu Gln Ser Met Tyr Gly Cys Asp Val Gly Pro Asp Gly Arg Leu
5 10 15
Leu Arg Gly His Asp Gln Tyr Ala Ile
20

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:15

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:beta-pleated sheet of MHC Class I

(B) LOCATION:99-113

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:13:

Tyr Gly Cys Asp Val Gly Pro Asp Gly Arg Leu Leu Arg Gly His
5 10 15

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:16

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:beta-pleated sheet of MHC Class I

(B) LOCATION:96-111

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:14:

Gln Ser Met Tyr Gly Cys Asp Val Gly Pro Asp Gly Arg Leu Leu Arg
5 10 15

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:19

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:beta-pleated sheet of MHC Class I

(B) LOCATION:100-118

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:15:

Gly Cys Asp Val Gly Pro Asp Gly Arg Leu Leu Arg Gly His Asp
5 10 15
Gln Tyr Ala Ile

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:24

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:alpha-helical structure of MHC Class I

(B) LOCATION:64-87

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:16:

Thr Gln Ile Tyr Lys Ala His Ala Gln Thr Asp Arg Glu Ser Leu
5 10 15
Arg Asn Leu Arg Gly Tyr Tyr Asn Gln
20

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:16

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:alpha-helical structure of MHC Class I

(B) LOCATION:64-79

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:17:

Thr Gln Ile Tyr Lys Ala His Ala Gln Thr Asp Arg Glu Ser Leu
5 10 15
Arg

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:9

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:alpha-helical structure of MHC Class I

(B) LOCATION:79-87

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:18:

Arg Asn Leu Arg Gly Tyr Tyr Asn Gln
5

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:40

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:19:

```
Ile Leu Gly Thr Ser Val Val Gly Ala Asp Glu Glu Gln Gly Asn
                5                   10                  15
Xaa Leu Gln Ser Met Tyr Gly Cys Asp Val Gly Pro Asp Gly Arg
                20                  25                  30
Leu Leu Arg Gly His Asp Gly Tyr Ala Ile
                35                  40
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:40

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:20:

```
Asn Gly Gln Glu Glu Asp Ala Gly Val Val Ser Thr Gly Leu Ile
                5                   10                  15
Xaa Leu Gln Ser Met Tyr Gly Cys Asp Val Gly Pro Asp Gly Arg
                20                  25                  30
Leu Leu Arg Gly His Asp Gly Tyr Ala Ile
                35                  40
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:40

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:21:

```
Asn Gly Gln Glu Glu Asp Ala Gly Val Val Ser Thr Gly Leu Ile
                5                   10                  15
Xaa Ile Ala Tyr Gly Asp His Gly Arg Leu Leu Arg Gly Asp Pro
                20                  25                  30
Gly Val Asp Cys Gly Tyr Met Ser Gln Leu
                35                  40
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:40

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:22:

```
Ile Leu Gly Thr Ser Val Val Gly Ala Asp Glu Glu Gln Gly Asn
                5                   10                  15
Xaa Ile Ala Tyr Gly Asp His Gly Arg Leu Leu Arg Gly Asp Pro
                20                  25                  30
Gly Val Asp Cys Gly Tyr Met Ser Gln Leu
                35                  40
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:15

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:SEQ ID NO:36 linked to Asp at position 6

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:23:

Asn Gln Gly Glu Glu Asp Ala Gly Val Val Ser Thr Gly Leu Ile
5 10 15

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:15

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:SEQ ID NO:12 linked to Glu at position 5 and SEQ ID NO:13 linked to Ala at position 7

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:24:

Asn Gly Gln Glu Glu Asp Ala Gly Val Val Ser Thr Gly Leu Ile
5 10 15

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:16

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Leu at position 6 is also amino acid residue 95 of SEQ ID NO:12 with residues 96-118 of SEQ ID NO:12

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:25:

Asn Gly Gln Glu Glu Leu Lys Ala Gly Val Val Ser Thr Gly Leu Ile
5 10 15

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:43

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 1 represents SEQ ID NO:12

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:26:

Xaa Gly Gly Gly Gly Ser Asn Gly Gln Glu Glu Lys Ala Gly Val
5 10 15
Val Ser Thr Gly Leu Ile Gly Gly Gly Lys Tyr Val Gly Ala Lys
20 25 30
Glu Glu Ala Thr Phe Ser Leu Val Asp Phe Ala Ser Asp
35 40

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:37

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:27:

Asn Gly Gln Glu Glu Asp Ala Gly Val Val Ser Thr Gly Leu Ile
5 10 15
Gly Gly Gly Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu
20 25 30
Glu Lys Ala Gly Val Tyr Lys
35

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:37

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:SEQ ID NO:13 is linked to Asp at position 6 and SEQ ID NO:15 is linked to Glu at position 5 and SEQ ID NO:13 is linked to Ala at position 7

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:28:

Asn Gly Gln Glu Glu Asp Ala Gly Val Val Ser Thr Gly Leu Ile
5 10 15
Gly Gly Gly Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu
20 25 30
Glu Lys Ala Gly Val Tyr Lys
35

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:35

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:29:

```
Asn Gly Gln Glu Glu Xaa Ala Gly Val Val Ser Thr Gly Leu Ile
                  5                  10                  15
Xaa Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys
                 20                  25                  30
Ala Gly Val Tyr Lys
                 35
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:35

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:30:

```
Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala
                  5                  10                  15
Gly Val Tyr Lys Xaa Asn Gly Gln Glu Glu Xaa Ala Gly Val Val
                 20                  25                  30
Ser Thr Gly Leu Ile
                 35
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:33

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:31:

Asp Leu Leu Lys Asn Gly Glu Arg Xaa Glu Lys Val Glu Xaa Asp
5 10 15
Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala Gly
20 25 30
Val Tyr Lys

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:33

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:32:

Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala
5 10 15
Gly Val Tyr Lys Xaa Asp Leu Leu Lys Asn Gly Glu Arg Xaa Glu
20 25 30
Lys Val Glu

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:35

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 10 represents one or more amino acids other than single Lys; Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:31:

Asp Leu Leu Lys Asn Gly Glu Arg Xaa Glu Lys Val Glu Xaa Asp
5 10 15
Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala Gly
20 25 30
Val Tyr Lys

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:33

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:32:

Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala
5 10 15
Gly Val Tyr Lys Xaa Asp Leu Leu Lys Asn Gly Glu Arg Xaa Glu
20 25 30
Lys Val Glu

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:35

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 10 represents one or more amino acids other than single Lys; Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:33:

```
Ile Leu Gly Thr Ser Val Val Gly Ala Xaa Glu Glu Gln Gly Asn Xaa
                5                   10                  15
Asp Ser Ala Phe Asp Val Leu Ser Phe Thr Ala Glu Glu Lys Ala Gly
            20                  25                  30
Val Tyr Lys
        35
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:35

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa as position 6 represents one or more amino acid residues other than a single Lys; Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:34:

```
Asn Gly Gln Glu Glu Xaa Ala Gly Val Val Ser Thr Gly Leu Ile
                5                   10                  15
Xaa Lys Tyr Val Gly Ala Lys Glu Glu Ala Thr Phe Ser Leu Val
            20                  25                  30
Asp Phe Ala Ser Asp
        35
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:35

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:Xaa at position 10 represents one or more amino acid residues other than Lys; Xaa at position 16 represents a divalent spacer

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:35:

```
Ile Leu Gly Thr Ser Val Val Gly Ala Xaa Glu Glu Gln Gly Asn
                5                   10                  15
Xaa Lys Tyr Val Gly Ala Lys Glu Glu Ala Thr Phe Ser Leu Val
                20                  25                  30
Asp Phe Ala Ser Asp
                35
```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:16

(B) TYPE:amino acid

(C) TOPOLOGY:linear

(ii) MOLECULE TYPE:peptide

(v) FRAGMENT TYPE:internal

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(C) IDENTIFICATION METHOD:

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION:SEQ ID NO:36:

```
Gly Cys Asp Val Gly Pro Asp Gly Arg Leu Leu Arg Gly His Asp Gln
                5                   10                  15
```